Practitioner's Docket No.: 889_001 ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Jiro Kanie

Serial No.:	10/826,165	Group Art Unit:	1618
Filed:	April 16, 2004	Examiner:	Young, Micah Paul
Conf. No.:	8549		

For: ENTERNAL NUTRITION PRODUCT AND METHOD FOR PREPARING THE SAME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION OF EFS TRANSMISSION

I hereby certify that this paper is being transmitted via EFS to the Patent and Trademark Office on April 15, 2008.

Christina M. Bersani

DECLARATION UNDER 37 CFR §1.132

Sir:

I, Jiro Kanie, a citizen of Japan hereby declare and state:

1. I have a PhD. degree in medicine which was conferred upon me by Department of Geriatrics of Nagoya University Graduate School of Medicine, in 65 Tsurumai-cho, Showa-ku, 466-8550 Nagoya, Aichi, Japan, in 1998.

2. I have been running my own hospital since 2000, and I have had a total of 18 years of work and research experience in Geriatrics.

3. I am a member of :

- THE JAPAN GERIATRICS SOCIETY
- HOME HEALTH CARE, ENDOSCOPIC THERAPY AND QUALITY OF LIFE
- THE JAPANESE SOCIETY OF GASTROENTEROLOGY
- JAPAN GASTROENTEROLOGICAL ENDOSCOPY SOCIETY
- THE JAPANESE SOCIETY OF INTERNAL MEDICINE
- THE JAPAN MEDICAL ASSOCIATION

4. I am the inventor of the above-identified patent application and I am familiar with the references applied in the Office Action mailed November 16, 2007.

5. The following is evidence of secondary considerations in support of patentability that the PTO must consider and which sufficiently to establishes the non-obviousness of the present invention.

(A) Corresponding Japanese Patent

Prior to the filing of the present U.S. patent application, I filed a corresponding Japanese patent application, which was allowed and issued as Japanese Patent No. 3516673. The JPO recognized the novelty and non-obviousness of the present invention.

(B) Existing Patent License

I have received offers to license my Japanese Patent from the Japanese pharmaceutical company "Otsuka Pharmaceutical Factory Inc. This company is one of the affiliates of Otsuka Pharmaceutical Co. Ltd. (see Appendix A attached hereto for more company information).

After successful negotiation, the Japanese Patent was licensed to Otsuka Pharmaceutical Factory, Inc. as a non-exclusive licensee, and the company received from the JPO, after request, a Patent Registration for the purpose of registering the grant of non-exclusive license. The original version of the Patent registration and an English translation thereof are attached hereto as Appendix B.

(C) Royalty Rate

The royalty rate on the sales applied to the licensee for the Japanese patent is 2%. This rate is about the average, and is expected to be larger compared to the cost of litigation, pre-license investigation by the licensees, etc. Therefore, the licensing considerations are persuasive in demonstrating that the licensee recognizes the novelty, non-obviousness and usefulness of the present invention, and also believes the Japanese patent is valid.

Indeed, the establishment of the licensing shows that the present invention has been recognized as being novel and commercially important in the related industry, and the validity of the Japanese patent is not easily challenged. The same holds true for the claimed invention in the present U.S. application, which is not obvious based on the prior art of record.

(D) Ongoing Negotiation for additional Patent Licenses

Another Japanese company has made an offer for license of the above-stated Japanese patent. This company is "San-Ei Gen F.F.I., Inc." More information about this company is included in the attachment in Appendix C hereto.

That company has also shown a great interest with respect to its desire to practice the Japanese patent. We are presently in the course of negotiating a licensing agreement.

(E) Peer Recognition in the Related Field (publication of inventor's reports in U.S. medical treatises)

As indicated in the arguments which were presented to the U.S. PTO in the Amendment filed on August 29, 2005, the entire remarks of which are incorporated herein, I have co-authored several published reports on the claimed invention. Two of these reports were previously submitted to the U.S. PTO.

One of the two reports is titled "Prevention of Late Complications by Half-Solid Enternal Nutrients in Percutaneous Endiscopic Gastrostomy Tube Feeding," published on pp. 417-419 of the clinical section of Vol. 50, No. 6, 2004 of "Gerontology (International Journal of Experimental, Clinical and Behavioral Gerontology)," by Kerger Publishers. A copy of this article is attached as Appendix D hereto.

The other article is titled "Prevention of Gastro-Esophageal Reflux by an Application of Half-solid Nutrients in Patients with Perculaneous Endoscopic Gastronomy Feeding," published on pp. 466-467 of Vol. 52: Issue 3, March 2004 of "The Journal of the American Geriatrics Society," by Blackwell Publishing. A copy of this article is attached as Appendix E hereto.

(F) Long felt but unresolved need

As indicated in the specification of the present application, there has been a strong need to prevent dysphagic patients, especially elderly patients, from suffering from gastro-esophageal reflux when enternal nutrition products are administered to the patients via

a tube. The need has been long felt, but has been heretofore unresolved. The present invention, however, solves this long felt need and has been academically praised and commercially recognized and implemented.

6. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: April 15, 2008 Jiro Kanie

Jiro KANIE

Attachments: Appendices A-F

Company Profile

I. Otsuka Pharmaceutical Factory, Inc.

a. Basic Information

Head Office :	115 Kuguhara, Tateiwa, Muya-cho, Naruto, Tokushima 772-8601, Japan
Phone :	+81-88-685-1151
Facsimile:	+81-88-685-7667
Established:	September 1, 1921
President:	Ichiro Ostuka
Capital:	80 million yen
Annual Sales:	95,510 million yen (as of September 30, 2005)
Number of Employee:	2,460 (as of September 30, 2005)
Business Description:	Manufacturing and sale of pharmaceutical and nutritional products

b. License Agreement

Licensed Patent	JP3516673 (which is substantially identical to the claimed invention in the present U.S. patent application)
Licensed Product	Enteral Nutrition Product
Target Customers for the Licensed Product	·patients with dysphagia ·elder people who have difficulty in swallowing
Royalty Rate	2% on the sales of the patented products
Term of This Agreement	from July 9, 2007 to July 9, 2010

Appendix A

c. Patent Legacy Information

The Number of Patents (including Patent Applications)	1813 (from 1993 to 2008)
The Number of Patents (inluding Patent Applications) related to Enteral Nutrition Products	11 (from 1993 to 2008)

d. Additional Information

Parent Company:	Otsuka Pharmaceutical Co., Ltd.
Head Office :	2-9 Kanda-Tsukasamachi, Chiyoda-ku, Tokyo 101-8535, JAPAN
Phone :	+81-3-3292-0021
Established:	August 10, 1964
President:	Tatsuo Higuchi
Capital:	6.791 billion yen
Number of Employee:	5,225 (as of March 31, 2007)
Business Description:	Manufacturing, distributing, exporting, and importing of pharmaceuticals, clinical testing equipment, medical equipment, food products, cosmetics, and other related products
Business Premises	17 branch offices, 51 district offices (in Japan)
Reserch Facilities	18 divisions in 5 locations
Clinical Research	2 divisions
Factories	6 locations

Appendix A

(translation)

Notice of Patent Registration

(seal)
Japan Patent Office

Date of Acceptance: November 2, 2007
Acceptance No.: 009867
Person Entitled to the Registration: Otsuka Pharmaceutical Factory, Inc.
Registered on: November 15, 2007

Note

Item Number	Patent Number	Supplementary Note	Purpose
1	JP3516673	001	【Grant of Non-Exclusive License】

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NAGOYA-SHI, JAPAN 460-0002

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Made on: November 15, 2007 00037

Appendix B

特　許　登　録　済　通　知　書

特　許　庁

受付年月日　平成１９年１１月　２日　　受付番号　００９８６７

登録権利者　株式会社大塚製薬工場

平成１９年１１月１５日　登録

記

項番	特　許　番　号	順位付記	目　的
1	３５１６６７３	001	【通常実施権の設定】

〒４６０－０００２

住所　愛知県名古屋市中区丸の内２－１７－１２　丸の内エステートビル４０３号

氏名　来栖和則　　様

平成１９年１１月１５日　作成　　00037

Appendix B

Company Profile

Ⅱ. San-Ei Gen F.F.I., Inc.

a. Basic Information

Head Office :	1-4-9, Hirano-machi, Chuo-ku, Osaka 540-8688 JAPAN
Phone :	+81-6-6202-3751
Facsimile:	+81-6-6202-3770
Established:	September, 1938
President:	Takashige Shimizu
Capital:	1,800 million yen
Annual Sales:	64,800 million yen (April 2005 - March 2006))
Products & Servuces:	Food ingredients, Foods, Food materials, Quasi-drugs, Industrial chemicals

b. Patent Legacy Information

The Number of Patents (including Patent Applications)	1,054 (from 1993 to 2008)
The Number of Patent (including Patent Applications) related to a semi-solidifying agent	119 (from 1993 to 2008)

Appendix C

Clinical Section

Gerontology

Gerontology 2004;50:417–419
DOI: 10.1159/000080181

Received: August 12, 2003
Accepted: February 15, 2004

Prevention of Late Complications by Half-Solid Enteral Nutrients in Percutaneous Endoscopic Gastrostomy Tube Feeding

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Key Words
Percutaneous endoscopic gastrostomy · Enteral nutrients, half-solid · Gastroesophageal reflux

Abstract
Background: Percutaneous endoscopic gastrostomy feeding is accompanied by unique complications, which are not easily controlled. ***Objective:*** In an attempt to decrease complications, we used half-solid nutrients for percutaneous endoscopic gastrostomy feeding in an 85-year-old woman. The patient had been receiving enteral nutrients via percutaneous endoscopic gastrostomy, and we examined whether this approach can reduce complications. She presented with regurgitation of enteral nutrients and recurrent respiratory infections. ***Methods:*** Half-solid enteral nutrients, prepared by mixing liquid enteral nutrients with agar powder, were administered via percutaneous endoscopic gastrostomy. ***Results:*** Symptoms of gastroesophageal reflux disappeared immediately after the start of half-solid enteral nutrient feeding. ***Conclusion:*** Gastroesophageal reflux and leakage, two intractable late complications of percutaneous endoscopic gastrostomy tube feeding, can be alleviated by the solidification of enteral nutrients. Since this method allows quick administration of nutrients, it is also expected to help prevent the occurrence of decubitus ulcers and reduce the burden to the caregiver.

Introduction

Feeding via a percutaneous endoscopic gastrostomy (PEG) tube is a safe and efficient method for patients who cannot maintain adequate oral intake. PEG feeding is accompanied, however, by unique complications which are not easily controlled. The administration of liquid nutrients is often accompanied by complications such as vomiting and diarrhea, although these complications may be minimized if the patient is sitting up during the administration or if the nutrients are administered at a slower rate. Nevertheless, these methods do not completely succeed in eliminating these common complications, and may require the patients and their caregivers to have great patience. In addition, maintaining the same position for many hours may worsen the conditions of patients who have pressure ulcers. Here we report a case in which, by

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Appendix D

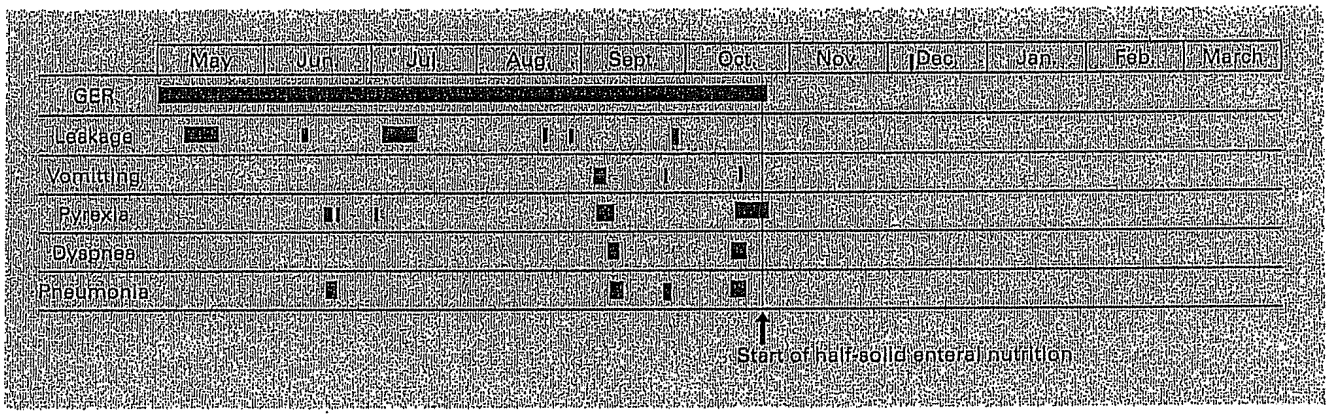

Fig. 1. Reduction of symptoms after half-solid enteral nutrition via PEG.

simply solidifying nutrients, the symptoms due to gastroesophageal reflux (GER) after PEG tube placement were relieved, and the leakage of nutrients from the PEG tube insertion site was alleviated.

Methods

An 85-year-old woman presented with regurgitation of enteral nutrients and recurrent respiratory infections after PEG placement. The patient suffered a cerebral infarction, and underwent PEG insertion on May 4, 2001, at a local hospital. After commencing PEG tube feeding, the following symptoms repeatedly occurred: regurgitation of the enteral feed; leakage of nutrients from the PEG tube insertion site; vomiting followed by pyrexia; dyspnea during the administration of nutrients, and pneumonia confirmed by chest X-ray. The patient often showed facial signs of discomfort during the feed administration. Liquid enteral nutrients were given in a sitting position at all times.

As the complications gradually became more frequent in occurrence, on October 21, 2001, we commenced giving her half-solid enteral nutrients which were prepared by mixing market-available enteral nutrients and agar powder. Half-solid nutrients were prepared by mixing 5 g agar powder with 500 ml liquid nutrients diluted with the same volume of water (1,000 ml total volume). The mixture was distributed into 50-ml syringes and kept in a refrigerator until it was administered via the PEG tubing. The mixture was not liquefied in the stomach due to body temperature. The administration of half-solid nutrients was made by injecting them into the stomach en bloc (injection time <5 min). The patient was not forced to remain in a sitting position during and after the administration.

Results

The symptoms, other than pyrexia, disappeared immediately after the administration of half-solid nutrients, and pyrexia vanished 2 weeks later. Also, the signs of discomfort during the feed administration were no longer noted. We followed the patient for up to 6 months after the start of the half-solid enteral nutrients, and observed no recurrence of the symptoms (fig. 1). At present (February 2004), the patient still remains in a stable condition and no longer suffers from the complications observed before the commencement of half-solid nutrients.

Discussion

PEG feeding is accompanied by unique complications, which occur over a long-term clinical course [1–3]. An increase in vomiting is one of the most common complications [4]. GER is clinically manifested by recurrent vomiting or aspiration. The mechanism by which GER increases in frequency has not yet been clarified.

Ogawa et al. [5, 6] suggested that since the stomach cannot move independent of the abdominal wall after the formation of a gastric fistula, enteral nutrients remain in the stomach longer, thereby increasing the chance of GER. Gastrin, a potent facilitator of peristaltic movement, may not be sufficiently induced by the distension of the stomach seen with slow infusion rates of liquid nutrients. Thus enhanced GER may eventually result. Since the nutrients can be administered in a short time by

Appendix D

our method (<5 min), the stomach wall is expected to be distended to a greater degree and thus stimulate peristaltic movement.

Another disadvantage of slow feed infusion is that patients are forced to remain in a sitting position for long periods while the nutrients are administered, which is unfavorable in terms of the prevention of decubitus ulcers, which are commonly found in patients with PEG feeding.

One of the late complications after PEG tube placement is leakage from the PEG tube insertion site. This is a difficult problem to cope with. There are two causes of leakage: inappropriate fixation of the bumper (including the so-called buried bumper syndrome [7]), and a decrease in the elasticity of the fistular opening, which develops over a long period after PEG placement [8]. The leakage resulting from a decrease in elasticity is intractable. Simply increasing the tube diameter cannot solve this problem [7, 9]. We found, however, that solidification of the enteral nutrients alleviated the leakage in the present case. This may simply be explained by the fact that the solidified nutrients could not be leaked out by the intragastric pressure through the narrow gap between the fistular pore and the tube.

So far, we have administered half-solid nutrients to 17 patients with PEG feeding and followed up the patients for 6 months. During the observation period, we confirmed significant reductions in the complications observed before the commencement of the half-solid nutrients (data not shown).

In conclusion, our experience indicates that the use of half-solid nutrients in PEG feeding and their rapid administration can substantially reduce the risk of GER and may eventually contribute to a reduction in complications as well as an improvement in the quality of life of the patients and their caregivers.

References

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Appendix D

Prevention of gastro-esophageal reflux by an application of half-solid nutrients in patients with percutaneous endoscopic gastrostomy feeding

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To the Editor: Although percutaneous endoscopic gastrostomy (PEG) feeding is widely used as a convenient method for long-term nutritional support[1], administration of liquid nutrients is often accompanied by complications such as vomiting or diarrhea. Vomiting, which may result in critical condition by aspiration, is presumably caused by gastro-esophageal reflux (GER). Therefore, we used half-solid nutrients for PEG feeding and examined whether this approach can reduce GER.

Seventeen patients (mean age±SD; 79.9±10.5), who were on PEG feeding participated in this study. Written informed consent was obtained from all patients. Either liquid or half-solid nutrients were administered via PEG tubing in a randomized order. Half-solid nutrients were prepared by mixing 5g of agarose with 500ml of liquid nutrients diluted with the same volume of water. Incidence of GER was assessed by computed tomography scan (CT) of the esophagus. Liquid nutrients were administered over 15 minutes in portions of 400ml containing 20ml of the water-soluble contrast material, Gastrografin (methylglucamine diatrizonate). The half-solid nutrients were administered by bolus injections of the same volume of nutrients, which were contained separately in 50ml syringes. Thirty minutes after the administration, CT scan was performed in 1cm thick slices of the esophageal portion. GER was confirmed if the Hounsfield number exceeded 100 in each slice examined. A Hounsfield number of 100 was employed because it can unequivocally distinguish the mixture of the nutrients containing contrast material from the esophageal and other surrounding tissues. The CT images were assessed by a radiologist, who was not informed of the type of nutrients used. Statistical comparison of the incidence of GER between the two types of nutrients was made using Mc Nemar's test.

GER was confirmed in 10 out of the 17 subjects (58.8%) when they received liquid nutrients. By contrast, when they received half-solid nutrients, only 4 of 17 subjects (23.5%) showed the evidence of GER from their CT findings. ($\chi^2 = 6.0$, df = 1, p = 0.014, by Mc Nemar's test) (Table 1).

The advantages of PEG feeding over nasogastric feeding has been discussed elsewhere albeit there have been some complications reported.[2] Among the complications, vomiting can be a cause of fatal aspiration due to a reflux of the administered nutrients.[3] The tubing used for PEG feeding has made it possible to apply half-solidified nutrients, which we hypothesized would cause less reflux from the stomach.[4] As expected, we observed less evidence of GER when using half-solid nutrients than when using liquid nutrients. We also confirmed that solidifying nutrients using agarose did not clog the tube as compared to liquid nutrients. Continuous infusion and careful observation of the patient's symptoms are considered necessary to reduce the risk of GER in PEG feeding. Also the patients are advised to remain in a sitting position during administration, which

Journal of the American Geriatrics Society 2004; 52(3): 466-467

Appendix E

may increase the risk of developing or exacerbating decubitus ulcers. Thus, this pilot study suggests that the use of rapid administration of half-solid nutrients in PEG feeding can reduce the risk of GER substantially, and may eventually contribute to a reduction of complications as well as to the improvement in the quality of life for patients and their cargivers.

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2. Dwolatzky T, Berezovski S, Friedmann R et al. A prospective comparison of the use of nasogastric and percutaneous endoscopic gastrostomy tubes for long-term enteral feeding in older people. *Clin Nutr* 2001; 20: 535-540.
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Table 1. Occurrence of gastro-esophageal reflux by liquid and half-solid nutrients

Age	Sex	Clinical profile	gastro-esophageal reflux		Range of reflux		Distance from the EC junction	
			Liquid	Half-solid	Liquid	Half-solid	Liquid	Half-solid
82	F	Dementia	(-)	(-)				
81	F	Dementia	(-)	(-)				
90	F	Dementia	(+)	(+)	7	6	13	13
53	F	Cerebral infarction	(-)	(-)				
87	F	Dementia	(+)	(-)	4		13	
80	F	Dementia	(+)	(+)	9	4	9	10
82	M	Dementia	(+)	(+)	4	4	13	13
87	F	Cerebral infarction	(+)	(-)	1		4	
84	M	Cerebral infarction	(+)	(-)	12		15	
68	F	Cerebral infarction	(+)	(-)	13		13	
82	F	Dementia	(-)	(-)				
89	F	Cerebral infarction	(-)	(-)				
91	F	Cerebral infarction	(+)	(-)	1		2	
84	F	Cerebral infarction	(+)	(+)	15	10	15	10
87	F	Dementia	(-)	(-)				
68	M	Cerebral infarction	(-)	(-)				
64	M	Cerebral hemorrhage	(+)	(-)	5		8	
			10 (58.8%)	4 (23.5%)*				

Range of reflux: Number of slices where contrast materials were confirmed in the esophagus
Distance from the EC junction:
Distance from the esophageal-cardiac junction to the upper limit of the slices where contrast materials were confirmed (cm)
* Statistical significance by Mc Nemar's test ($\chi^2 = 6.0$; df = 1, p = 0.014)

Appendix E